IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of

Peart et al.

Serial No. 10/759,280

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Confirmation No. 6861

Group Art Unit: 1616

Examiner: Alstrum Acevedo, James Henry

For: *"Δ^9 TETRAHYDROCANNABINOL (Δ^9 THC) SOLUTION METERED DOSE INHALERS AND METHODS OF USE"*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF JEFFRY G. WEERS UNDER 37 C.F.R. 1.132

Dear Sir:

1. I am currently employed by Nektar Therapeutics (formerly Inhale Therapeutic Systems, Inc.) (which has licensed the above-identified patent application), where I have been employed since 1999. I hold the position of Senior Director, Pharmaceutical Development. I am an expert in the field of aerosolized medication and have particular knowledge and understanding of hydrofluoroalkane (HFA) propellants and the formulation challenges presented in the generation of HFA based metered dose inhalers (MDIs). I have experience over the last 20+ years as Research Director in colloid-based research, including extensive experience with a wide variety of colloidal systems including: micelles, microemulsions, emulsions, liposomes, microbubbles, foams, liquid crystals, suspensions, and aerosols. I have a Bachelor of Science degree, with Honors, in Chemistry from University of Puget Sound (1980) and a Ph.D. in Chemistry from University of California at Davis (1985).

2. I have reviewed the above-identified patent application, the pending claims, the office action dated December 28, 2005 which has been entered in this application, and the references

relied upon by the Examiner for the obviousness rejections. It is my opinion that the invention, as claimed, would not have been obvious to one of ordinary skill in the art over any combination of references cited by the Examiner.

3. I am familiar with the level of skill of one of ordinary skill in the art in the field of aerosolized propellant based pharmaceutical formulations used in MDIs. Typically, the individual would have had at least a bachelor's degree in pharmaceutics, but more often he or she would have had an advanced degree such as a Ph.D. In addition, he or she would have had at least eight years hands on experience in working with propellants such as chlorofluorocarbons (CFCs) and HFAs such as 1,1,1,2-tetrafluorethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227). Furthermore, he or she would be familiar with at least some of the many articles written by Dr. P.R. Byron in such journals as *Pharmaceutical Research* and *Int. J. Pharm.*, as well as the Respiratory Drug Delivery Proceedings edited by Dr. Byron for CRC Press, Inc. One of ordinary skill in the art would recognize the many challenges that have confronted the MDI industry in view of international treaties calling for the phase out of ozone depleting propellants such as CFCs.

4. One of ordinary skill in the art would have recognized that solubilizing drugs in HFA propellants is a difficult and challenging hurdle in the preparation of acceptable MDI formulations. It would be particularly surprising and unexpected to one of ordinary skill in the art that the solubility of THC in HFA propellants is high. For example, this high solubility is particularly striking when comparing the solubility of common bronchodilators, corticosteroids and surfactants in HFA 134a. The solubility of butixocort propionate in HFA 134a is 0.02% w/w (see McNally et al. U.S. Patent 5,653,961, cited by the Examiner in the office action dated December 28, 2005); the solubility of beclomethasone dipropionate is 0.03% w/w (see Verveat et al., *Int. J. Pharm.* 186:13-30 (1999)); and the solubility of flunisolide hemihydrate is less than 0.0006% w/w. The results in HFA 227 are similar. Solubilities of surfactants in HFA propellants is detailed in Blondino et al., *Drug Dev. Ind. Pharm.* 24:935-945 (1998)). The solubility of oleic acid is less than 0.02% w/w, and of sorbitan trioleate is less than 0.02% w/w.

In order to collect reliable solubility data, one of ordinary skill in the art would know that he or she needs to wait a period of time after combining the medication with the propellant in

order to undergo dissolution and reach equilibrium. The above-identified patent application demonstrates in Table 3 that the solubility of THC in HFA propellants is an order of magnitude higher than either the hydrophobic or hydrophilic compounds quoted above, and Table 4 demonstrates that the concentration of dissolved THC remains stable for long periods of time under extreme test conditions. Prior reports have shown similar solubilities to the extremely hydrophobic THC discussed in the above-identified patent application only for hydrophilic compounds (see Blondino 1998 and Vervaet 1999). Hydrophobic compounds (e.g., butixocort) are expected to show solubilities in HFA propellant about 1/10 that which has been discovered by the inventors in THC.

5. One of ordinary skill in the art would know that in order to be a viable formulation for use in a metered dose inhaler the following criteria, among others, must be met:

A) The first option for the formulation of an MDI would be to prepare a suspension formulation (in this instance the drug would not be soluble in the propellant (e.g., HFA 134a). However, for a resinous substance such as THC which could not be processed to produce 2-3μm sized particles, suspension formulations are not an option. In this instance, solution formulations are the only option and the drug must be soluble in the propellant (e.g., HFA 134a). Furthermore, the drug must be soluble in high enough quantities that the MDI can provide therapeutically effective doses to the patient.

B) The formulation must be able to produce a significant percentage of respirable droplets when aerosolized (i.e., droplets less than 10μm in diameter).

C) The formulation must be chemically and physically stable for a significant period of time (i.e., there must be a useful "shelf-life" for the product, while still maintaining suitable aerosol characteristics).

A variety of factors impact on each of these three criteria, and if any of these factors is out of kilter, producing a viable MDI will be impossible.

6. The above-identified application would demonstrate to one of ordinary skill in the art the unexpected result that therapeutically feasible respirable doses of THC are possible in HFA propellants due to the drug's high solubility in HFA 134a and HFA 227, both of which are high vapor pressure liquified gases. While the addition of ethanol would be expected to increase THC

solubility, one of ordinary skill in the art would know that ethanol concentrations should be minimized for toxicological reasons. Thus, one of ordinary skill in the art would assume that without significant levels of solvent, not enough THC could be solubilized to provide therapeutic doses; however, the drug's newly discovered high solubility in HFAs overcomes this problem.

Respirable doses ranging from 0.25 to 1mg are believed to be necessary for THC's therapeutic efficacy in inhalation. MDI metering values usually meter by volume in the range of 25-100 µl. This corresponds to 30-120 mg of propellant. The table below shows the relationship between the needed concentration of THC in solution and the dose metered by an MDI with a 100 µl metering valve.

Concentration of THC in Solution

HFA 134a MDI	THC Metered Dose
0.2% w/w	0.24 mg (as can be seen from Table 3 of the application this is possible in HFA 134a alone (0% ethanol)
1.0% w/w	1.2 mg (requires less than 5% ethanol–see Table 3)
2.0% w/w	2.4 mg (requires less than 10% ethanol)
3.0% w/w	3.6 mg (requires less than 10% ethanol)
4.0% w/w	4.8 mg (requires less than 15% ethanol)
5.0% w/w	6.0 mg (requires less than 15% ethanol)

It would be clear to one of ordinary skill in the art that the results in this table which correlate to the data presented in Table 3 of the application that the high concentrations in solution that result from both the use of HFA propellants and ethanol as a co-solvent enable large metered doses of THC to be achieved. For example, from the results reported in the above-identified application, it can be seen that the solubility of THC in 5% ethanol/95% HFA 134a is 1.585% w/w and this enables an MDI with a metered dose of 1.10 mg to provide a particle (respirable) fraction of more than 20% even with a non-optimized spray nozzle.

7. For background purposes, it should be understood that one of ordinary skill in the art would know that MDIs meter fixed volumes of liquid formulations containing ingredients with

different degrees of volatility. These fixed volumes are atomized at the nozzle provided the formulation has sufficient vapor pressure. High vapor pressure MDI formulations produce smaller, more respirable aerosols (see, Moren, *Int. J. Pharm.* 1:213-218 (1978)). The liquid in the MDI occupies 95-100% of the sprayed formulation and thus it is the nature of this liquified propellant (some ingredients will vaporize on leaving the nozzle, while others will not) and the speed with which it is propelled by its own vapor that dictate the droplet size formed at the spray nozzle of the actuator (see, Polli, *J. Pharm. Sci.* 58:484-486 (1969)). Inclusion of large concentrations of surfactants or ethanol is not advisable because they create large non-respirable aerosols. For example, it is known that the use of ethanol as a co-solvent to produce drug solutions in propellants results in producing large, less respirable aerosols because of the low volatility of this co-solvent in CFC propellants (see Bell, *J. Pharm. Pharmac.* 25:32P-36P (1973)). In addition, high non-volatile drug concentrations increase aerosol size and decrease the respirable fraction of the dose (see Byron, Respiratory Drug Delivery, Chapter 7, CRC Press 1990).

THC is a high dose, non-volatile drug. Thus, a significant challenge in formulating an aerosolizable composition of THC is to minimize the concentration of non-volatile ingredients (e.g., cosolvents, surfactants) in order to maximize the respirability of the aerosol leaving the nozzle; smaller aerosols being more respirable.

8. A metered dose represents the product of the metered volume supplied by the MDI and the drug concentration in the liquified formulation. Thus, increased concentrations enabled decreased metered volumes and vice versa to achieve the same dosage. Increasing the metered volume or drug concentration tends to increase particle size of the emitted aerosol because more energy is necessary to evaporate the larger propellant volume and large drug concentrations raise the non-volatile constituent concentration and thereby the size of the resulting aerosol.

The available data on the commercially available oral form of THC, Marinol[R], indicates that an administered dose of 2.5-5 mg is effective but only 10% of this dose is bioavailable or absorbed systemically. The inventors of the present application have demonstrated that THC is well absorbed following inhalation (see Lichtman, *Eur. J. Pharm.* 399: 141-149 (2000)). If it is assumed that there is 100% availability of the respirable dose (i.e., aerodynamic diameters less

than or equal to 5.8μm), then usable MDI products would need to deliver doses of 0.25-0.5 mg in one or two puffs. If there is a need for higher doses, this range might be extended to 1 mg. In 1998 and following, before this invention, metering valves for inhalation purposes ranged between 25 μl and 100 μl. Thus, the metering volume and the required respirable dose define the useable concentration range for the drug. A significant discovery reported in the above-referenced application is that the compositions will be suitable for providing THC at therapeutically effective dosages. This can be seen by the table below.

Valve Volume (μl)	Concentration (% w/w) [a]	THC Dose (mg) metered[b]; emitted[c]; and respirable[d]	Number of puffs	Total Repirable Dose (mg)
25	2% (II)	0.6;0.5;0.125	2	0.25
25	2% (II)	0.6;0.5;0.125	4	0.50
25	4% (III)	1.2;1.0;0.25	1	0.25
25	4%(III)	1.2;1.0;0.25	2	0.50
50	1% (I)	0.6;0.5;0.125	2	0.25
50	1% (I)	0.6;0.5;0.125	4	0.5
50	2% (II)	1.2;1.0;0.25	1	0.25
50	2%(II)	1.2;1.0;0.25	2	0.5
50	4% (III)	2.4;2.0;0.5	1	0.5
50	4%(III)	2.4;2.0;0.5	2	1.0
100	1%(I)	1.2;1.0[e];0.25	1	0.25
100	1%(I)	1.2;1.0[e];0.25	2	0.5
100	2%(II)	2.4; 2.0;0.5	1	0.5
100	2%(II)	2.4; 2.0;0.5	2	1.0
100	4% (III)	4.8;4.0;1.0	1	1.0
100	0.2% (IV)	0.24[f];.0.2;0.14	2	0.28

a) Roman numerals indicate likely formulations I=1.0% THC, 4.95% ethanol, 94.05%HFA 134a;

II=2.0% THC, 9.8% ethanol, 88.2% HFA 134a; III=4.0% THC, 14.4% ethanol, 81.6% HFA 134a; IV=0.2% THC, 99.8% HFA 134a (percentages are by weight throughout)

b) Metered Dose is the mass of THC delivered through the valve

c) Emitted Dose is the mass of the THC delivered through the actuator mouthpiece. Theoretical estimate assuming actuator mouthpiece retention as seen in Table 4b of the above-identified application.

d) Respirable Dose is the mass of the THC comprising droplets with aerodynamic diameters $\leq 5.8\mu m$. Theoretical estimate assuming that $\leq 5.8\mu m$ dose fraction was unchanged by drug concentration or metering volume.

e) Approximated from Table 4b of the above-identified patent application

f) ethanol free formulation containing THC at 90% of its solubility in pure HFA 134a, showing that a total respirable dose of 0.28 mg is possible given two puffs through an actuator bearing modified spray nozzle that has a smaller diameter chosen to produce smaller aerosols.

9. The above demonstrates that the compositions which have been discovered by the applicants can be used to provide effective doses of THC to a patient. There has been a long felt need for being able to provide THC to patients in a safe and efficacious manner, and the claimed products and methods satisfy that need.

The extreme hydrophobic nature of THC has been a major stumbling block in developing pharmaceutically effective formulations. Despite the considerable effort that has been dedicated to developing a medically viable THC delivery system, none of these endeavors has met with success except for orally administered THC. Marinol[R] (dronabinol) capsules, an oral form of THC, the chief psychoactive cannabinoid constituent of marijuana, was the only available cannabinoid for the alleviation of nausea and emesis in patients requiring chemotherapy for cancer as well as for anorexia associated with weight loss in AIDS patients. In addition, THC was believed to possess efficacy for a variety of other conditions including analgesia for chronic pain and reducing the muscle spasticity associated with multiple sclerosis. However, the pharmacokinetics of the drug profoundly limited its clinical efficacy. In particular, dronabinol undergoes extensive first-pass hepatic metabolism resulting in only 10-20% of the administered dose reaching systemic circulation (see Unimed Pharmaceutics I (20010 Product Monograph;

Marinol (dronabinol), in pp. 1-50). Moreover, the time course of dronabinol is slow with an onset of action occurring at approximately 0.5 to 1 hours and peak effects occurring at 2 to 4 hours. Importantly, the rapid onset of action is critical to controlling nausea and emesis and particularly delayed chemo-induced nausea and emesis that is not adequately controlled by standard antiemetic agents.

In contrast, the pharmacokinetics of tetrahydrocannabinol following inhalation is considerably more favorable than the oral route of administration. First pass metabolism is eliminated and the onset of action is on the order of minutes thus allowing patients to titrate their dose better than the oral route of administration. The recognition of the advantages of the inhalation route of administration over the oral route combined with the unavailability of a tetrahydrocannabinol inhalation device have led to strong public support that physicians should have the option to prescribe marijuana to relieve the suffering of seriously or terminally ill patients. Consequently, California passed a referendum in 1996 known as Proposition 215 which allows seriously ill Californians to obtain and use marijuana for medical purposes without criminal prosecution (several other states have passed similar laws).

In January 1997, the increasing public pressure to permit the use of marijuana as medicine prompted the White House Office of National Drug Control Policy to ask the Institute of Medicine (IOM) to conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. In the report that followed, the IOM concluded that there is a therapeutic potential for cannabinoid drugs, mainly Δ^9-THC, for alleviation of chronic pain, control of nausea and vomiting, stimulation of appetite, and for the relief of muscle spasticity associated with multiple sclerosis (see Joy et al., *Marijuana and Medicine*, National Academy Press 1999, Washington, D.C.). However, the report also acknowledged that the oral route of administration hampers the effectiveness of THC because of the slow absorption and the patient's desire to better control dosing. In addition, the report cautioned that marijuana is a crude THC delivery system that simultaneously delivers harmful chemicals in addition to THC. Thus, IOM recommended the development of rapid-onset, reliable and safe delivery THC delivery systems.

Despite the fact that the interest in THC dates back nearly thirty years when efforts were

focused on developing a CFC propellant MDI to deliver THC to the lungs for treating asthma, no acceptable delivery systems of inhalation THC have been developed. The invention described in the above-identified application provides a formulation which allows efficacious doses of respirable THC to be delivered in accurate and reproducible fashion, and with no significant degradation of the drug occurring following storage in extreme conditions. As such, it represents an important solution to a long felt and complex problem, and is surprising in view of the failures of CFC based solutions.

10. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Jeffry G. Weers

27 Mar 06
Date